Kidney360

Safety of Gadolinium-Based Contrast Agents in Patients with Stage 4 and 5 Chronic Kidney Disease: a Radiologist's Perspective

Erik V. Soloff and Carolyn L. Wang

KIDNEY360 1: 123–126, 2020. doi: https://doi.org/10.34067/KID.0000502019

Gadolinium-based contrast agents (GBCAs) have been used for contrast-enhanced magnetic resonance imaging (MRI) since 1988 with >450 million intravenous GBCA doses administered worldwide and overall have had an excellent safety record (1,2). Numerous studies have demonstrated the benefit of GBCAs for a variety of diagnostic indications including improving sensitivity and specificity for malignancy, demyelination, central nervous system malignancy, and infection (3–7). Initially, it was thought that GBCAs would be safer than iodinated contrast media for patients with kidney disease because they are less nephrotoxic at clinically administered doses (8). Although some case reports have linked AKI to GBCA administration, most cases involve patients with advanced renal disease or diabetes and with doses that exceed US Food and Drug Administration (FDA) recommendations (8).

The safety of GBCAs in patients with kidney disease came into question in 2006 when a strong association was found between the use of GBCAs in patients with severe kidney disease and the development of nephrogenic systemic fibrosis (NSF) (9–11). NSF results in fibrosis of the skin and internal organs and can be fatal. A conclusive mechanism of causation for NSF has not been determined. Several mouse models of NSF have been developed to investigate the underlying pathophysiology; however, they tend to use doses which are higher than those approved by the FDA and older linear agents (12–14). A confounding issue is that many people with severe kidney disease received multiple exposures to GBCAs and did not develop NSF. Conversely, patients with only one administration of a GBCA have developed NSF (15,16). It is unclear if this could at least partially relate to interspecies differences. Multiple factors may contribute, most notably patient-specific risk factors and the stability of the GBCA, which is a result of its molecular structure. Based on clinical reports, the most important factor appears to be severely reduced renal function. The most prevalent belief is that delayed clearance of GBCAs allows gadolinium to dissociate from the chelating agent and deposit in tissue (17), resulting in fibrous connective tissue and plaque formation. This theory was proposed in part because of the strong association of NSF with lower-stability linear nonionic GBCAs gadoversetamide and gadodiamide, and an ionic linear agent gadopentetate dimeglumine (17). These three GBCAs are now classified as "group 1" agents by the American College of Radiology (ACR) and "high-risk" agents by the Canadian Association of Radiology (CAR) (Table 1). Several studies have shown that use of these lower-stability GBCAs in patients with normal kidney function or mild-to-moderate CKD (stage 3; eGFR 30–59 ml/min per 1.73 m^2) is without clinically significant risk of NSF (8). However, they remain absolutely contraindicated in patients with AKI or stage 4 or 5 CKD (eGFR <30 ml/min per 1.73 m^2).

After becoming aware of NSF in patients with severe renal disease and its association with GBCAs, many institutions adopted restrictive policies regarding the use of GBCAs and several studies demonstrated a significant decline in incidence of NSF (18–20). Wang *et al.* (21) demonstrated no new cases of NSF among 52,954 contrast-enhanced magnetic resonance examinations, including 6490 patients with an eGFR <60 ml/min per 1.73 m^2. A 2019 systematic review of the literature found 639 patients with biopsy-confirmed NSF were administered almost exclusively nonionic linear agents at high doses (>0.1 mmol/kg). Of these patients, only seven confirmed cases of NSF occurred after 2008 (22). The authors concluded that regulatory actions and practice changes have been effective in reducing the incidence of NSF.

The ACR has further categorized the remaining GBCAs into group 2 and group 3 agents that have few if any unconfounded cases of NSF, with group 2 GBCAs having greater published safety data in patients with severe kidney disease (23). Group 2 GBCAs include all macrocyclic agents and one newer linear ionic agent, whereas group 3 GBCAs comprises only one GBCA, which is a newer linear agent (Table 1). Both gadobenate dimeglumine (group 2) and gadoxetate disodium (group 3) have partial hepatobiliary excretion and protein binding, which may help explain their apparent lower risk of NSF.

Several studies have evaluated the safety of gadoterate meglumine in patients with acute kidney disease or CKD (19,24–25). A 2019 systematic review and meta-analysis of 2700 studies to evaluate the pooled risk of NSF in patients with stage 4 and 5 CKD who

Radiology Department, University of Washington, Seattle, Washington

Correspondence: Dr. Carolyn L. Wang, Radiology Department, University of Washington, 1959 NE Pacific Street, Seattle, WA 98195. Email: wangcl@uw.edu

Table 1. Current or previously approved gadolinium-based contrast agents and their manufacturer, chemical structure and ionicity, American College of Radiology classification, and Canadian Association of Radiologists risk assessment

Gadolinium Agent	Manufacturer	Chemical Structure	ACR Classification	CAR Risk Assessment
Gadodiamide	GE Healthcare	Linear nonionic	Group 1	High risk
Gadoversetamide	Guerbet	Linear nonionic	Group 1	High risk
Gadopentetate dimeglumine	Bayer AG	Linear ionic	Group 1	High risk
Gadobutrol	Bayer Healthcare/Bayer AG	Macrocyclic nonionic	Group 2	Low risk
Gadoteridol	Bracco Diagnostics	Macrocyclic nonionic	Group 2	Low risk
Gadoterate meglumine	Guerbet	Macrocyclic ionic	Group 2	Low risk
Gadobenate dimeglumine	Bracco Diagnostics	Linear ionic	Group 2	Medium risk
Gadoxetate disodium	Bayer Healthcare	Linear ionic	Group 3	Medium risk

ACR, American College of Radiology; CAR, Canadian Association of Radiologists.

received group 2 GBCAs determined that the risk was likely no greater than 0.07% (26). The authors concluded that the potential diagnostic harms of withholding group 2 GBCAs for indicated examinations may outweigh the risk of developing NSF.

Gadolinium retention in the brain, bone, and soft tissues has emerged as another potential risk of GBCA administration (1,27–28), which has resulted in several lawsuits claiming effects related to gadolinium deposition. Unlike NSF, gadolinium retention occurs in patients with normal kidney function (27–28). Studies have shown that the degree of retention is dependent on the stability of the GBCA, similar to the cases of NSF. Specifically, linear nonionic agents retain more gadolinium than linear ionic agents, and linear ionic agents retain more gadolinium than macrocyclic agents (29–30). The exact clinical effects of this deposition are currently unknown. Limited patient self-reported data of nonallergic-like effects associated with GBCA exposure have been published (31–32). Forslin *et al.* (33) performed a retrospective 18-year longitudinal cohort study in 23 subjects with multiple sclerosis (MS) exposed to GBCAs and 23 healthy age- and sex-matched control subjects who underwent unenhanced MRI. The results showed that increased signal intensity in the dentate nucleus (DN) in the patients with MS was associated with lower verbal fluency scores at neuropsychological testing (33). This group more recently published data suggesting that linear, but not macrocyclic, GBCA administration is associated with higher relaxation rates in a dose-dependent manner and that higher relaxation in certain regions is associated with cognitive impairment but not physical disability or fatigue in MS (34). Unfortunately, both studies are limited by the same confounding variable of MS pathology in the study cohorts. In distinction, Vymazal *et al.* (35) performed neurologic and neuropsychological testing of four patients with glioblastoma multiforme, all of whom had in excess of 50 contrast-enhanced MRI scans. They all showed increased T1 signal in the DN and globus pallidum. During follow-up for 14 years, none developed signs of neurologic or neuropsychological effects from the GBCA retention (35). Cocozza *et al.* (36) retrospectively evaluated 74 patients with relapsing-remitting MS and those with DN T1-weighted hyperintensity showed similar changes in the expanded disability status scale compared with subjects without DN high-signal intensity. At present, no adverse effects have been conclusively, scientifically linked to the retention of gadolinium in patients. To our knowledge, no case-controlled prospective studies have confirmed a causal link between gadolinium retention and symptoms.

Both the ACR and CAR have published guidelines on the use of GBCAs in patients with kidney disease (23,37). Both organizations recognize that MRI scans with contrast provide useful diagnostic information and that NSF, a serious and debilitating disease, has a strong association with certain GBCAs. They also recognize that effective screening of patients at greatest risk has essentially eliminated new cases of NSF. Finally, although many investigations have confirmed that free gadolinium deposition occurs in patients with all types of GBCAs, it does not have a predilection for people with impaired renal function, and the long-term effects and potential for complications have not yet been established. Ultimately, the decision whether to administer GBCAs must be made by referring physicians in consultation with radiologists to identify the most appropriate examination to answer the clinical question. The benefits of improved diagnostic accuracy must be compared with the very small, albeit not zero, risk for NSF in patients with severe kidney disease and the currently unknown clinical risk of gadolinium deposition elsewhere. The radiology community remains committed to studying the potential risks and has developed a roadmap for investigation (2). Advances in noncontrast-enhanced MRI sequences continue, however, some clinical indications still require contrast enhancement for correct interpretation (38).

GBCA use during MRI scanning has had an excellent safety record over the past three decades. Despite a probable correlation between development of NSF after the use of group 1 agents in patients with stage 4 and 5 CKD, current data supports the safe use of the group 2 agents at recommended doses in patients with AKI, CKD stage 4 or 5, or those on dialysis. Although the safety of these agents may be questioned in animal studies, the benefit of using them in making accurate and important clinical diagnoses has far outweighed the small theoretical risk of developing NSF.

Author Contributions

E. Soloff and C. Wang conceptualized the study, wrote the original draft, and reviewed and edited the manuscript.

Disclosures

E. Soloff and C. Wang have nothing to disclose.

References

1. Ramalho J, Semelka RC, Ramalho M, Nunes RH, AlObaidy M, Castillo M: Gadolinium-based contrast agent accumulation and toxicity: An update. *AJNR Am J Neuroradiol* 37: 1192–1198, 2016
2. McDonald RJ, Levine D, Weinreb J, Kanal E, Davenport MS, Ellis JH, Jacobs PM, Lenkinski RE, Maravilla KR, Prince MR, Rowley HA, Tweedle MF, Kressel HY: Gadolinium retention: A research roadmap from the 2018 NIH/ACR/RSNA workshop on Gadolinium Chelates. *Radiology* 289: 517–534, 2018
3. Klerkx WM, Bax L, Veldhuis WB, Heintz APM, Mali WP, Peeters PH, Moons KG: Detection of lymph node metastases by gadolinium-enhanced magnetic resonance imaging: Systematic review and meta-analysis. *J Natl Cancer Inst* 102: 244–253, 2010
4. Schelfout K, Van Goethem M, Kersschot E, Colpaert C, Schelfhout AM, Leyman P, Verslegers I, Biltjes I, Van Den Haute J, Gillardin JP, Tjalma W, Van Der Auwera JC, Buytaert P, De Schepper A: Contrast-enhanced MR imaging of breast lesions and effect on treatment. *Eur J Surg Oncol* 30: 501–507, 2004
5. Smith TE, Steven A, Bagert BA: Gadolinium deposition in neurology clinical practice. *Ochsner J* 19: 17–25, 2019
6. Graif M, Bydder GM, Steiner RE, Niendorf P, Thomas DG, Young IR: Contrast-enhanced MR imaging of malignant brain tumors. *AJNR Am J Neuroradiol* 6: 855–862, 1985
7. Seute T, Leffers P, ten Velde GP, Twijnstra A: Detection of brain metastases from small cell lung cancer: Consequences of changing imaging techniques (CT versus MRI). *Cancer* 112: 1827–1834, 2008
8. Ledneva E, Karie S, Launay-Vacher V, Janus N, Deray G: Renal safety of gadolinium-based contrast media in patients with chronic renal insufficiency. *Radiology* 250: 618–628, 2009
9. Kuo PH, Kanal E, Abu-Alfa AK, Cowper SE: Gadolinium-based MR contrast agents and nephrogenic systemic fibrosis. *Radiology* 242: 647–649, 2007
10. High WA, Ayers RA, Chandler J, Zito G, Cowper SE: Gadolinium is detectable within the tissue of patients with nephrogenic systemic fibrosis. *J Am Acad Dermatol* 56: 21–26, 2007
11. Sadowski EA, Bennett LK, Chan MR, Wentland AL, Garrett AL, Garrett RW, Djamali A: Nephrogenic systemic fibrosis: Risk factors and incidence estimation. *Radiology* 243: 148–157, 2007
12. Do C, Drel V, Tan C, Lee D, Wagner B: Nephrogenic systemic fibrosis is mediated by myeloid C-C chemokine receptor 2. *J Invest Dermatol* 139: 2134–2143.e2, 2019
13. Do C, Ford B, Lee DY, Tan C, Escobar P, Wagner B: Gadolinium-based contrast agents: Stimulators of myeloid-induced renal fibrosis and major metabolic disruptors. *Toxicol Appl Pharmacol* 375: 32–45, 2019
14. Sieber MA, Pietsch H, Walter J, Haider W, Frenzel T, Weinmann HJ: A preclinical study to investigate the development of nephrogenic systemic fibrosis: A possible role for gadolinium-based contrast media. *Invest Radiol* 43: 65–75, 2008
15. Collidge TA, Thomson PC, Mark PB, Traynor JP, Jardine AG, Morris ST, Simpson K, Roditi GH: Gadolinium-enhanced MR imaging and nephrogenic systemic fibrosis: Retrospective study of a renal replacement therapy cohort. *Radiology* 245: 168–175, 2007
16. Thomsen HS, Morcos SK, Almén T, Bellin MF, Bertolotto M, Bongartz G, Clement O, Leander P, Heinz-Peer G, Reimer P, Stacul F, van der Molen A, Webb JA; ESUR Contrast Medium Safety Committee: Nephrogenic systemic fibrosis and gadolinium-based contrast media: Updated ESUR contrast medium safety committee guidelines. *Eur Radiol* 23: 307–318, 2013
17. Idée JM, Fretellier N, Robic C, Corot C: The role of gadolinium chelates in the mechanism of nephrogenic systemic fibrosis: A critical update. *Crit Rev Toxicol* 44: 895–913, 2014
18. Altun E, Martin DR, Wertman R, Lugo-Somolinos A, Fuller ER 3rd, Semelka RC: Nephrogenic systemic fibrosis: Change in incidence following a switch in gadolinium agents and adoption of a gadolinium policy--report from two U.S. universities. *Radiology* 253: 689–696, 2009
19. Chrysochou C, Power A, Shurrab AE, Husain S, Moser S, Lay J, Salama AD, Kalra PA: Low risk for nephrogenic systemic fibrosis in nondialysis patients who have chronic kidney disease and are investigated with gadolinium-enhanced magnetic resonance imaging. *Clin J Am Soc Nephrol* 5: 484–489, 2010
20. Altun E, Semelka RC, Cakit C: Nephrogenic systemic fibrosis and management of high-risk patients. *Acad Radiol* 16: 897–905, 2009
21. Wang Y, Alkasab TK, Narin O, Nazarian RM, Kaewlai R, Kay J, Abujudeh HH: Incidence of nephrogenic systemic fibrosis after adoption of restrictive gadolinium-based contrast agent guidelines. *Radiology* 260: 105–111, 2011
22. Attari H, Cao Y, Elmholdt TR, Zhao Y, Prince MR: A systematic review of 639 patients with biopsy-confirmed nephrogenic systemic fibrosis. *Radiology* 292: 376–386, 2019
23. ACR Committee on Drugs and Contrast Media: ACR Manual on Contrast Media Version 10.3, American College of Radiology, 2018. Available at: https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Accessed December 6, 2019
24. Janus N, Launay-Vacher V, Karie S, Clement O, Ledneva E, Frances C, Choukroun G, Deray G: Prevalence of nephrogenic systemic fibrosis in renal insufficiency patients: Results of the FINEST study. *Eur J Radiol* 73: 357–359, 2010
25. Deray G, Rouviere O, Bacigalupo L, Maes B, Hannedouche T, Vrtovsnik F, Rigothier C, Billiouw JM, Campioni P, Ferreiros J, Devos D, Alison D, Glowacki F, Boffa JJ, Marti-Bonmati L: Safety of meglumine gadoterate (Gd-DOTA)-enhanced MRI compared to unenhanced MRI in patients with chronic kidney disease (RESCUE study). *Eur Radiol* 23: 1250–1259, 2013
26. Woolen SA, Shankar PR, Gagnier JJ, MacEachern MP, Singer L, Davenport MS: Risk of Nephrogenic Systemic Fibrosis in Patients With Stage 4 or 5 Chronic Kidney Disease Receiving a Group II Gadolinium-Based Contrast Agent: A Systematic Review and Meta-analysis. *JAMA Intern Med* 2019 10.1001/jamainternmed.2019.5284
27. McDonald RJ, McDonald JS, Kallmes DF, Jentoft ME, Murray DL, Thielen KR, Williamson EE, Eckel LJ: Intracranial gadolinium deposition after contrast-enhanced MR imaging. *Radiology* 275: 772–782, 2015
28. Kanda T, Fukusato T, Matsuda M, Toyoda K, Oba H, Kotoku J, Haruyama T, Kitajima K, Furui S: Gadolinium-based contrast agent accumulates in the brain even in subjects without severe renal dysfunction: Evaluation of autopsy brain specimens with inductively coupled plasma mass spectroscopy. *Radiology* 276: 228–232, 2015
29. Stojanov D, Aracki-Trenkic A, Benedeto-Stojanov D: Gadolinium deposition within the dentate nucleus and globus pallidus after repeated administrations of gadolinium-based contrast agents-current status. *Neuroradiology* 58: 433–441, 2016
30. US Food & Drug Administration: FDA Drug Safety Communication: FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue. White Oak, MD, US Food & Drug Administration, 2017. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-identifies-no-harmful-effects-date-brain-retention-gadolinium. Accessed December 6, 2019
31. Burke LM, Ramalho M, AlObaidy M, Chang E, Jay M, Semelka RC: Self-reported gadolinium toxicity: A survey of patients with chronic symptoms. *Magn Reson Imaging* 34: 1078–1080, 2016
32. Semelka RC, Ramalho M, Jay M, Hickey L, Hickey J: Intravenous calcium-/zinc-diethylene triamine penta-acetic acid in patients with presumed gadolinium deposition disease: A preliminary report on 25 patients. *Invest Radiol* 53: 373–379, 2018
33. Forslin Y, Shams S, Hashim F, Aspelin P, Bergendal G, Martola J, Fredrikson S, Kristoffersen-Wiberg M, Granberg T: Retention of gadolinium-based contrast agents in multiple sclerosis: Retrospective analysis of an 18-year longitudinal study. *AJNR Am J Neuroradiol* 38: 1311–1316, 2017
34. Forslin Y, Martola J, Bergendal Å, Fredrikson S, Wiberg MK, Granberg T: Gadolinium retention in the brain: An MRI relaxometry study of linear and macrocyclic gadolinium-based contrast agents in multiple sclerosis. *AJNR Am J Neuroradiol* 40: 1265–1273, 2019
35. Vymazal J, Krámská L, Brožová H, Růžička E, Rulseh AM: Does serial administration of gadolinium-based contrast agents affect patient neurological and neuropsychological status? Fourteen-year follow-up of patients receiving more than fifty contrast

administrations [published online ahead of print October 30, 2019]. *J Magn Reson Imaging*
36. Cocozza S, Pontillo G, Lanzillo R, Russo C, Petracca M, Di Stasi M, Paolella C, Vola EA, Criscuolo C, Moccia M, Lamberti A, Monti S, Brescia Morra V, Elefante A, Palma G, Tedeschi E, Brunetti A: MRI features suggestive of gadolinium retention do not correlate with Expanded Disability Status Scale worsening in Multiple Sclerosis. *Neuroradiology* 61: 155–162, 2019
37. Schieda N, Blaichman JI, Costa AF, Glikstein R, Hurrell C, James M, Jabehdar Maralani P, Shabana W, Tang A, Tsampalieros A, van der Pol C, Hiremath S: Gadolinium-based contrast agents in kidney disease: Comprehensive review and clinical practice guideline issued by the Canadian association of radiologists. *Can Assoc Radiol J* 69: 136–150, 2018
38. Falk Delgado A, Van Westen D, Nilsson M, Knutsson L, Sundgren PC, Larsson EM, Falk Delgado A: Diagnostic value of alternative techniques to gadolinium-based contrast agents in MR neuroimaging-a comprehensive overview. *Insights Imaging* 10: 84, 2019